



## **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**

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## Plasma HIV-1 RNA (Viral Load) and CD4 Count Monitoring (Last updated May 1, 2014; last reviewed May 1, 2014)

HIV RNA (viral load) and CD4 T lymphocyte (CD4) cell count are the two surrogate markers of antiretroviral treatment (ART) responses and HIV disease progression that have been used for decades to manage and monitor HIV infection.

Viral load is a marker of response to ART. A patient's pre-ART viral load level and the magnitude of viral load decline after initiation of ART provide prognostic information about the probability of disease progression.<sup>1</sup> The key goal of ART is to achieve and maintain durable viral suppression. Thus, the most important use of the viral load is to monitor the effectiveness of therapy **after** initiation of ART.

Measurement of CD4 count is particularly useful **before** initiation of ART. The CD4 cell count provides information on the overall immune function of an HIV-infected patient. The measurement is critical in establishing thresholds for the initiation and discontinuation of opportunistic infection (OI) prophylaxis and in assessing the urgency to initiate ART.

The management of HIV-infected patients has changed substantially with the availability of newer, more potent, and less toxic antiretroviral (ARV) agents. In the United States, ART is now recommended for all HIV-infected patients regardless of their viral load or CD4 count. In the past, clinical practice, which was supported by treatment guidelines, was generally to monitor both CD4 cell count and viral load concurrently. However, because most HIV-infected patients in care now receive ART, the rationale for frequent CD4 monitoring is weaker. The roles and usefulness of these two tests in clinical practice are discussed in the following sections.

### ***Plasma HIV-1 RNA (Viral Load) Monitoring***

Viral load is the most important indicator of initial and sustained response to ART (**AI**) and should be measured in all HIV-infected patients at entry into care (**AIII**), at initiation of therapy (**AIII**), and on a regular basis thereafter. For those patients who choose to delay therapy, repeat viral load testing while not on ART is optional (**CIII**). Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load (see [What to Start](#)). Commercially available HIV-1 RNA assays do not detect HIV-2 viral load. For further discussion on HIV-2 RNA monitoring in patients with HIV-1/HIV-2 co-infection or HIV-2 mono-infection, see [HIV-2 Infection](#).

Several systematic reviews of data from clinical trials involving thousands of participants have established that decreases in viral load following initiation of ART are associated with reduced risk of progression to AIDS or death.<sup>1-3</sup> Thus, viral load testing is an established surrogate marker for treatment response.<sup>4</sup> The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 log<sub>10</sub> copies/mL change). Optimal viral suppression is defined generally as a viral load persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used). However, isolated blips (viral loads transiently detectable at low levels, typically HIV RNA <400 copies/mL) are not uncommon in successfully treated patients and are not predictive of virologic failure.<sup>5</sup> Furthermore, the data on the association between persistently low level but quantifiable viremia (HIV RNA <200 copies/mL) and virologic failure is conflicting. One recent study showed an increased risk of subsequent failure at this level of viremia; however, the association was not observed in other studies.<sup>6-9</sup> These guidelines and the AIDS Clinical Trials Group (ACTG) now define virologic failure as a confirmed viral load >200 copies/mL—a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability<sup>10</sup> (see [Virologic Failure and Suboptimal Immunologic Response](#)).

Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it

may take longer. Recommendations on the frequency of viral load monitoring are summarized below:

- **After initiation of ART or modification of therapy because of virologic failure.** Plasma viral load should be measured before initiation of ART and within 2 to 4 weeks but no later than 8 weeks after treatment initiation or modification (**AIII**). The purpose of the measurements is to confirm an adequate initial virologic response to ART, indicating appropriate regimen selection and patient adherence to therapy. Repeat viral load measurement should be performed at 4- to 8-week intervals until the level falls below the assay's limit of detection (**BIII**).
- **In virologically suppressed patients in whom ART was modified because of drug toxicity or for regimen simplification.** Viral load measurement should be performed within 4 to 8 weeks after changing therapy (**AIII**). The purpose of viral load monitoring at this point is to confirm the effectiveness of the new regimen.
- **In patients on a stable, suppressive ARV regimen.** Viral load should be repeated every 3 to 4 months (**AIII**) or as clinically indicated to confirm continuous viral suppression. Clinicians may extend the interval to 6 months for adherent patients whose viral load has been suppressed for more than 2 years and whose clinical and immunologic status is stable (**AIII**).
- **In patients with suboptimal response.** The frequency of viral load monitoring will depend on clinical circumstances, such as adherence and availability of further treatment options. In addition to viral load monitoring, a number of additional factors, such as patient adherence to prescribed medications, suboptimal drug exposure, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen (see [Drug-Resistance Testing](#) and [Virologic Failure and Suboptimal Immunologic Response](#) sections).

## ***CD4 Count Monitoring***

The CD4 count is the most important laboratory indicator of immune function in HIV-infected patients. It is also the strongest predictor of subsequent disease progression and survival according to findings from clinical trials and cohort studies.<sup>11,12</sup> CD4 counts are highly variable; a significant change (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points. Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, is more expensive, and is **not routinely recommended** (**BIII**).

### **Use of CD4 Count for Initial Assessment**

CD4 count should be measured in all patients at entry into care (**AI**). It is the key factor in determining the need to initiate OI prophylaxis (see the [Adult Opportunistic Infection Guidelines](#))<sup>13</sup> and the urgency to initiate ART (**AI**) (see the [Initiating Antiretroviral Therapy in Antiretroviral-Naïve Patients](#) section of these guidelines). Although most OIs occur in patients with CD4 counts <200 cells/mm<sup>3</sup>, some OIs can occur in patients with higher CD4 counts.<sup>14</sup>

### **Use of CD4 Count for Monitoring Therapeutic Response**

The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued (see the [Adult Opportunistic Infection Guidelines](#))<sup>13</sup>. For most patients on therapy, an adequate response is defined as an increase in CD4 count in the range of 50 to 150 cells/mm<sup>3</sup> during the first year of ART, generally with an accelerated response in the first 3 months of treatment. Subsequent increases average approximately 50 to 100 cells/mm<sup>3</sup> per year until a steady state level is reached.<sup>15</sup> Patients who initiate therapy with a low CD4 count<sup>16</sup> or at an older age<sup>17</sup> may have a blunted increase in their counts despite virologic suppression.

## Frequency of CD4 Count Monitoring

ART is now recommended for all HIV-infected patients. In patients who remain untreated for whatever reason, CD4 counts should be monitored every 3 to 6 months to assess the urgency of ART initiation and the need for OI prophylaxis (**AIII**).

A repeat CD4 count 3 months after ART initiation will provide information regarding the magnitude of immune reconstitution (**AIII**). This repeat measurement is most important in patients who initiate ART with more advanced disease and require OI prophylaxis or treatment. In these patients, the magnitude and duration of CD4 count increase can be used to determine whether to discontinue OI prophylaxis and/or treatment as recommended in the guidelines for treatment and prophylaxis of opportunistic infections.<sup>13</sup> In this setting, and in the first 2 years following ART initiation, CD4 count can be monitored at 3- to 6-month intervals (**BII**).

The CD4 count response to ART varies widely, but a poor CD4 response in a patient with viral suppression is rarely an indication for modifying an ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 count provides limited information. Frequent testing is unnecessary because the results rarely lead to a change in clinical management. One retrospective study found that declines in CD4 count to  $<200$  cells/mm<sup>3</sup> are rare in patients with viral suppression and CD4 counts  $>300$  cells/mm<sup>3</sup>.<sup>18</sup> Similarly, the ARTEMIS trial found that CD4 monitoring had no clinical benefit in patients who had suppressed viral loads and CD4 counts  $>200$  cells/mm<sup>3</sup> after 48 weeks of therapy.<sup>19</sup> Furthermore, the risk of *Pneumocystis jirovecii* pneumonia is extremely low in patients on suppressive ART who have CD4 counts between 100 and 200 cells/mm<sup>3</sup>.<sup>20</sup> Although uncommon, CD4 count declines can occur in a small percentage of virologically suppressed patients and may be associated with adverse clinical outcomes such as cardiovascular disease, malignancy, and death.<sup>21</sup> An analysis of costs associated with CD4 monitoring in the United States estimated that reducing CD4 monitoring in treated patients from every 6 months to every 12 months could result in annual savings of approximately \$10 million.<sup>22</sup>

For the patient on a suppressive regimen whose CD4 count has consistently ranged between 300 and 500 cells/mm<sup>3</sup> for at least 2 years, the Panel recommends CD4 monitoring on an annual basis (**BII**). Continued CD4 monitoring for virologically suppressed patients whose CD4 counts have been consistently  $>500$  cells/mm<sup>3</sup> for at least 2 years may be considered optional (**CIII**). The CD4 count should be monitored more frequently, as clinically indicated, when there are changes in a patient's clinical status that may decrease CD4 count and thus prompt OI prophylaxis. Examples of such changes include the appearance of new HIV-associated clinical symptoms or initiation of treatment known to reduce CD4 cell count (e.g., interferon, chronic corticosteroids, or anti-neoplastic agents) (**AIII**). In patients who fail to maintain viral suppression while on ART, the Panel recommends CD4 count monitoring every 3 to 6 months (**AIII**) (see [Virologic Failure and Suboptimal Immunologic Response](#) section).

## Factors that Affect Absolute CD4 Count

The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4+ T lymphocytes. This absolute number may fluctuate in individuals or may be influenced by factors that may affect the total WBC count and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy<sup>23,24</sup> or co-infection with human T-lymphotropic virus type I (HTLV-1)<sup>25</sup> may cause misleadingly elevated CD4 counts. Alpha-interferon may reduce the absolute CD4 count without changing the CD4 percentage.<sup>26</sup> In all these settings, CD4 percentage remains stable and may be a more appropriate parameter to assess a patient's immune function.

**Table 4. Recommendations on the Indications and Frequency of Viral Load and CD4 Count Monitoring<sup>a</sup>**

Clinical Scenario	Viral Load Monitoring	CD4 Count Monitoring
Before initiating ART	At entry into care <b>(AIII)</b>  If ART initiation is deferred, repeat before initiating ART <b>(AIII)</b> .  In patients not initiating ART, repeat testing is optional <b>(CIII)</b> .	At entry into care <b>(AI)</b>  If ART is deferred, every 3 to 6 months <b>(AIII)</b> . <sup>b</sup>
After initiating ART	Preferably within 2 to 4 weeks (and no later than 8 weeks) after initiation of ART <b>(AIII)</b> ; thereafter, every 4 to 8 weeks until viral load suppressed <b>(BIII)</b> .	3 months after initiation of ART <b>(AIII)</b>
After modifying ART because of drug toxicities or for regimen simplification in a patient with viral suppression	4 to 8 weeks after modification of ART to confirm effectiveness of new regimen <b>(AIII)</b> .	Monitor according to prior CD4 count and duration on ART, as outlined below.
After modifying ART because of virologic failure	Preferably within 2 to 4 weeks (and no later than 8 weeks) after modification <b>(AIII)</b> ; thereafter, every 4 to 8 weeks until viral load suppressed <b>(BIII)</b> . If viral suppression is not possible, repeat viral load every 3 months or more frequently if indicated <b>(AIII)</b> .	Every 3 to 6 months <b>(AI)</b>
During the first 2 years of ART	Every 3 to 4 months <b>(AIII)</b>	Every 3 to 6 months <sup>a</sup> <b>(BII)</b>
After 2 years of ART (VL consistently suppressed, CD4 consistently 300-500 cells/mm <sup>3</sup> )	Can extend to every 6 months for patients with consistent viral suppression for ≥2 years <b>(AIII)</b> .	Every 12 months <b>(BII)</b>
After 2 years of ART (VL consistently suppressed, CD4 consistently >500 cells/mm <sup>3</sup> )		Optional <b>(CIII)</b>
While on ART with detectable viremia (VL repeatedly >200 copies/mL)	Every 3 months <b>(AIII)</b> or more frequently if clinically indicated. (See <a href="#">Virologic Failure and Suboptimal Immunologic Response</a> section)	Every 3 to 6 months <b>(AIII)</b>
Change in clinical status (e.g., new HIV clinical symptom or initiation of interferon, chronic systemic corticosteroids, or antineoplastic therapy)	Every 3 months <b>(AIII)</b>	Perform CD4 count and repeat as clinically indicated <sup>c</sup> <b>(AIII)</b>

<sup>a</sup> Monitoring of lymphocyte subsets other than CD4 (e.g., CD8, CD19) has not proven clinically useful, adds to costs, and is not routinely recommended **(BIII)**.

<sup>b</sup> Some experts may repeat CD4 count every 3 months in patients with low baseline CD4 count (<200–300 cells/mm<sup>3</sup>) before ART but every 6 months in those who initiated ART at higher CD4 cell count (e.g., >300 cells/mm<sup>3</sup>).

<sup>c</sup> The following are examples of clinically indicated scenarios: changes in a patient's clinical status that may decrease CD4 count and thus prompt initiation of prophylaxis for opportunistic infections (OI), such as new HIV-associated symptoms, or initiation of treatment with medications which are known to reduce CD4 cell count.

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